

REMARKS

Claims 1, 19, 22-23 and 68-134 are currently pending in this application. Claims 92-93, 95-97, 100-101, and 104-105 stand withdrawn. Claims 2-18, 20-21, and 24-67 are canceled. Claims 1, 68 and 82 are amended herein. Support for amended claims 1 and 68 can be found throughout the application as originally filed, *inter alia*, on page 49, lines 35-37. Support for amended claim 82 can be found throughout the application as originally filed, *inter alia*, on page 15, lines 32-34 and on page 51, lines 33-34. Upon entry of this response with amendments, claims 1, 19, 22-23 and 68-134 will remain pending.

Objections

New Matter Objection

The specification amendments filed December 02, 2002, are objected to under 35 U.S.C. § 132, as allegedly introducing new matter into the disclosure by way of amendment of Figure 2. Applicants submit herewith a replacement drawing sheet of Figure 2, labeled "replacement sheet", which removes the alleged new matter inclusion of "X" from the amendment of Figure 2. The replacement drawing sheet of Figure 2 also incorporates the remaining proposed amendments presented in the December 02, 2002 submission.

Sequence Requirements

Claims 80 and 81 were objected to as failing to comply with the requirements of the sequence rules of 37 C.F.R. § 1.821 (d) for failing to assign a sequence identifier to the heptad formula "a-b-c-d-e-f-g."

Applicants respectfully disagree and traverse this objection.

As stated *infra* regarding the rejections under 35 U.S.C. § 112, 2nd paragraph, Applicants submit that the identification of individual amino acid residues of a heptad repeat as residues a, b, c, d, e, f and g, respectively, is a standard nomenclature applied within this specific technical field which represents a repeating seven-residue unit. 37 C.F.R. § 1.821(a) of the sequence rules states that

[n]ucleotide and/or amino acid sequence as used in §§1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides...Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. 'Specifically defined' means those amino acids other than 'Xaa' and those nucleotide bases other than 'n' defined in accordance with the

World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25...

37 C.F.R. § 1.812(a)(emphasis added). Applicants submit that the representative heptad repeat formula "a-b-c-d-e-f-g" is specifically excluded from the "SEQ ID NO:" requirement of 37 C.F.R. § 1.821(d), as the representative heptad repeat formula contains fewer than four specifically defined amino acids. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to claims 80 and 81 for allegedly failing to comply with the "SEQ ID NO:" requirement of 37 C.F.R. § 1.821(d).

Rejections

Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 80 and 82 were rejected under 35 U.S.C. § 112, 2nd paragraph as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. The Office Action states that it is unclear whether the wording "a repeated heptad having the formula a-b-c-d-e-f-g" in claim 80 represents a single amino acid sequence or a collection of amino acid sequences. Furthermore, the Office Action takes the position that the term "substantially" in claim 82 renders the claim indefinite.

Applicants respectfully disagree and traverse this rejection.

According to the CCPA, "it is well established that 'claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest *reasonable* interpretation.'" In re Marosi, 710 F.2d 799, 802, 218 U.S.P.Q. (BNA) 289, 292 (CCPA 1983) (*quoting In re Okuzawa*, 537 F.2d 545, 548, 190 U.S.P.Q. (BNA) 464, 466 (CCPA 1976)).

"Definiteness problems often arise when words of degree are used in a claim. That some claim language may not be precise, however, does not automatically render a claim invalid." Seattle Box v Indus. Crating and Packing, 731 F.2d 818, 826, 221 USPQ 568, 573-574 (Fed. Cir. 1984). Regarding issues of definiteness of claim language, "the question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification." BJ Services v. Halliburton Energy Services, 338 F.3d 1368, 1372, 67 U.S.P.Q.2d (BNA) 1692 (Fed. Cir. 2003).

Regarding claim 82, Applicants submit that one of skill in the art would understand what was meant by the recitation of "substantially", a term of degree, in claim 82. However, for the purposes of expediting prosecution, Applicants have amended claim 82 to remove the offending language.

Regarding the rejection of claim 80 on indefiniteness grounds, Applicants submit that the identification of individual amino acid residues of a heptad repeat as residues a, b, c, d, e, f and g, respectively, is a standard nomenclature applied within this specific technical field which represents a repeating seven-residue (heptad) peptide sequence. Applicants submit that the nomenclature is in accordance with accepted scientific nomenclature applied in standard textbooks. The use of this nomenclature is seen clearly, for example, in Fig. 15-13 in the standard textbook "Biochemistry" (L. Stryer, Biochemistry, W.H. Freeman & Co. N.Y., 4th Ed., 1995, p. 396) (a copy of which is included herewith as Appendix A).

The recitation of the heptad repeat "a-b-c-d-e-f-g" is also clearly defined in the specification as originally filed, wherein it is stated that "it is according to the invention preferred that the TTSE comprises a repeated heptad having the formula a-b-c-d-e-f-g (N to C), wherein residues a and d generally are hydrophobic amino acids." See specification, page 22, lines 7-9. Representative use of the heptad repeat formula is visible in Figure 2, which demonstrates that the heptad repeat formula "a-b-c-d-e-f-g" is intended to reflect a repetitive heptad peptide sequence.

In light of the amendments and response provided herein, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 80 and 82 under 35 U.S.C. § 112, 2nd paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Rejections under 35 U.S.C. § 102

Claims 1, 19, 22 and 23 were rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by the disclosure of Hoppe *et al* (International Publication No. WO 95/31540). The Office Action states that Hoppe *et al* discloses a collectin neck region polypeptide or a variant or derivative thereof or a sequence of amino acids having an amino acid pattern or hydrophobicity profile which is the same as or similar to that of the collectin neck region and able to form a trimer, and also that Hoppe *et al* discloses heterologous moieties positioned at the N or C-terminus of collectin. The Office Action further points to a definition of a

tetranectin family member which encompasses proteins having homologous sequences to the disclosed neck region of human tetranectin, the disclosure of collectin is encompassed by claims drawn to tetranectin trimerising element.

Applicants respectfully disagree and traverse this rejection.

In order for a reference to anticipate under 35 U.S.C. § 102(b), the reference must disclose all elements of the claimed invention in a printed publication in this or a foreign country more than one year prior to the date of application for patent in the United States. *See* MPEP § 2133.

Because Hoppe *et al* does not disclose all elements of the claimed invention, Hoppe *et al* cannot stand as anticipatory art under 35 U.S.C. § 102 (b).

As an initial matter, Applicants note that the subject matter of claims 1, 19, 22 and 23 is directed to tetranectin trimerising structural elements. Tetranectin is a Ca^{2+} -binding trimeric protein belonging to a distinct class within the superfamily of C-type lectins. As described in detail in the specification, tetranectin is present in blood plasma and the extracellular matrix of certain tissues. *See* specification, p. 1, lines 11-19. The tetranectin group of proteins comprises tetranectin isolated from man and from mouse, and the highly related C-type lectin homologues isolated from the cartilage of cattle and reef shark.

The basic functional unit of tetranectin is now known to be homo-trimeric. In the monomeric subunits four structural domains can be distinguished; a N-terminal cysteine-rich domain, a collagen domain, a coiled-coil neck domain, and finally a C-type lectin domain (carbohydrate recognition domain, or CRD). The mature monomeric subunits consist of two structural domains, namely an N-terminal coiled-coil trimerisation domain (neck region) and a C-type lectin domain (carbohydrate recognition domain, CRD).

Collectins, as described by Hoppe *et al*, are a trimeric group of proteins which also belong to the superfamily of C-type lectins, and their functions are believed to include activity in innate defense systems. Several distinct types of collectins have been identified which include mannose binding protein (MBP), pulmonary surfactant proteins (SP-A and SP-D), bovine conglutinine, collectin liver 1 (CL-L1), and conglutinin (CL-43 and CL-46) (Wetering *et al*, 2004, Eur. J. Biochem. 271, 1229-1249). The basic functional unit of collectins is a trimer. In the monomeric subunits four structural domains can be distinguished: a N-terminal cysteine-rich domain; a collagen domain; a coiled-coil neck domain; and finally a C-type lectin domain (carbohydrate recognition domain, or CRD).

Although tetranectin and collectins both belong to the superfamily of C-type lectins, and both are capable of trimerizing, they are classified as two distinct and dissimilar groups of proteins. This can be seen, for example in Nielsen *et al.*, who state that

TN [tetranectin] contains a carbohydrate recognition domain (CRD) and, according to sequence homology studies, belongs to a distinct group of the C-type (calcium dependent) lectin superfamily, which also includes pancreatic stone protein (lithostathine) ...

Nielsen *et al.*, FEBS Letters, 412:388-396 (1997) (reference BC of the IDS filed April 23, 2001). Applicants submit that this demonstrates that homology studies show tetranectin belongs to a distinct group of the C-type lectin superfamily. Nielsen *et al.* continue by stating that

structure determinations of proteins of two other groups of C-type lectins have been reported: the group of collectins (three mannose-binding proteins, rat MBP from serum (MBP-A), rat MBP from liver (MBP-C), human MBP) [22-26], and of selectins (human E-selectin) [27].

Id at 388. It follows from Nielsen *et al.* that collectins belong to a different group of C-type lectins.

This clear division of collectin and tetranectin into separate protein groups has also been described by A.J. Day, for example in Figure 1, wherein collectins are categorised as "Group 3" and tetranectin is placed under "Miscellaneous vertebrate proteins". A.J. Day, "The C-type carbohydrate recognition domain (CRD) superfamily", Biochem. Soc. Trans., 22:83-87, (1994) (reference AK of the IDS filed April 23, 2001).

Applicants further provide herein as Appendix B, results from a BLAST sequence alignment analysis. The BLAST results demonstrate that there is no significant similarity between the amino acid sequences of the tetranectin trimerising structural element (TTSE; the neck region of tetranectin) and any of the various collectin neck-regions disclosed by Hoppe *et al.* Thus, when comparing the consensus sequence of Figure 2 with the collectin neck-regions disclosed by Hoppe *et al.*, p. 8, lines 1-8 (i.e., human SP-D; bovine SP-D; rat Sp-D; bovine conglutinin; and bovine collectin 43), no significant similarity exists between the sequences using the "BLAST 2 Sequences" analysis tool designed for direct comparison of two sequences (available via <http://www.ncbi.nlm.nih.gov/blast/bl2seq/bl2.html>). The alignment results of Appendix B are presented as follows: TTSE vs. human SP-D pages A1-3; TTSE vs. bovine SP-D pages B1-3; TTSE vs. rat Sp-D pages C1-3; TTSE vs. bovine

conglutinin pages D1-3; and TTSE vs. bovine collectin 43 pages E1-3 (BLOSUM62 was used as scoring matrix).

Although tetranectins and collectins both belong to the superfamily of C-type lectins and are related in terms of their primary and tertiary structure (both have a trimeric structure composed of three monomeric subunits comprising, i.a., a C-type lectin domain and a coiled-coil domain/neck-region), Applicants submit that the art demonstrates that they are classified as two separate groups of proteins. Additionally, sequence alignment analysis fails to demonstrate any significant similarity between the neck-region of collectins and the tetranectin trimerising structural element (the neck region of tetranectin) as defined in the present application.

Applicants have also amended claim 1 herein to recite that the trimeric complex remains as a trimer at a temperature of at least 60°C. This recitation has also been added to claim 68, from which claims 22 and 23 depend and incorporate said element. Hoppe *et al* fails to disclose polypeptide trimers having a thermal stability of at least 60°C, and therefore fails to teach all of the claim elements of claims 1 and 68, and all of the claims that depend therefrom.

Accordingly, Applicants respectfully submit that Hoppe *et al* does not teach all of the elements of claims 1, 19, 22 and 23, and therefore Hoppe *et al* cannot stand as anticipatory art under 35 U.S.C. § 102(b). Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 19, 22 and 23 under 35 U.S.C. § 102(b) as allegedly anticipated by Hoppe *et al*.

Rejections under 35 U.S.C. § 103

Claims 1, 19, 22-23, 68-91, 94, 98-99, 102-103 and 106-134 were rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Hoppe *et al* (WO 95/31540) in view of Thogersen *et al* (WO 94/18227), as evidenced by Kastrup *et al* and Nielsen *et al*.

More specifically, the Office Action states that Hoppe *et al* teach collectin as a trimerising molecule which can be fused to heterologous moieties on the N or C termini and that this trimerised structure is stable at temperatures of 50°C, but that Hoppe *et al* do not teach a tetranectin variant having a neck region that is at least 68% identical to the consensus sequence in figure 2. The Office Action states that Thogersen *et al* teach that tetranectin forms trimers in solution and in the crystal state, and that oligomerisation of the tetranectin

monomer is not interrupted by a heterologous moiety fused N-terminally to the tetranectin polypeptide. The Office Action also states that Kastrup *et al* teach that tetranectin forms trimers in solution and in the crystal state; that exons 1 and 2 of the tetranectin gene encode the structural feature of tetranectin responsible for trimerisation; and that Kastrup *et al* compares tetranectin with mannose binding protein, and points out that the neck region of mannose binding protein has been shown to be responsible for stabilisation of the conformation of the C-terminal part of the trimer.

The Office Action therefore holds that one of skill in the art would conclude that the sequence of Thogersen *et al* is a trimerising structural element having 100% sequence identity to the consensus sequence in figure 2, and that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the tetranectin neck region in place of the collectin neck region. Motivation is attributed to the teachings of Kastrup *et al* regarding trimerisation.

Applicants respectfully disagree and traverse this rejection.

Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. See M.P.E.P. § 716.02(a). Furthermore, "[e]vidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987), M.P.E.P. § 716.02 (a).

As stated *supra*, claims 1 and 68 claim a trimeric polypeptide complex which remains as a trimer at a temperature of at least 60°C. The inventors disclose in the application that the thermal stability of the tetranectin trimerising structural element is extremely high. For example, the specification states that

[t]he thermal stability of the tetranectin trimerisation module (as shown in the examples) is such that the trimer can be shown to exist even at about 60°C (Example 4, trimerised tetranectin) or at about 70°C (Example 3, trimerized ubiquitin), whereas a collectin trimer unit falls apart at about 50-55°C (WO 95/31540, Example 1, page 36 therein).

See specification, page 6, lines 1-6. The specification further states that

(a) a substantial part of the recombinant proteins exists in the oligomeric state of, and can be cross-linked as, trimeric molecules even at 70°C;

(b) SDS-PAGE analysis of reduced samples (Fig. 12) showed, that trimers are readily detectable even at 60°C; and

(c) a substantial amount of trimer molecules is present even at 70°C.

See specification, page 15, lines 32-34; page 49, lines 35-37; and page 51, lines 33-34, respectively.

Applicants submit that this improvement is surprising, unexpected, and significant. Hoppe *et al* teaches the synthesis of trimeric polypeptide complexes with a thermal stability having an upper limit of approximately 50-55°C. The thermal stability of the collectin neck region can be seen in Hoppe *et al* where it is stated that "[t]he structure disappears reversibly with increasing temperature and a thermal unfolding transition at 55°C was observed". See Hoppe *et al*, Example 1, page 36, lines 2-4. Hoppe *et al* further states that "[h]eterotrimerisation may be promoted by gentle heating, e.g., to about 50°C, then cooling to room temperature." *Id*, in Abstract. Thus, it is clear from Hoppe *et al*. that a trimeric complex based on the collectin neck region falls apart at temperatures above 50-55°C.

Tetranectin is, as explained *supra*, a protein that is substantially different from collectin, and many dissimilarities exist between the tetranectin trimerising structural element (the neck-region of tetranectin) and the neck-region of collectin. Accordingly, one of skill in the art would not necessarily expect to obtain similar results in a tetranectin trimerising structural element following the teachings relating to trimerising collectin. Furthermore, the inventors of the subject matter of the instant application have generated trimeric polypeptide complexes based on a tetranectin trimerising structural element (the neck region of tetranectin) which are thermally stable at temperatures as high as 60°C, and even as high as 70°C, approximately 10-40% higher temperature than Hoppe *et al* reported for a collectin-based trimeric complex.

The high thermal stability of the tetranectin trimerising structural element is an extremely useful and unexpected trait that enables the generation of trimeric polypeptide carrier complexes having a high thermal stability, and which do not disintegrate into monomer subunits at high temperatures (i.e., 60-70°C). Consequently, *via* the high thermal stability, the trimeric polypeptide complexes according to the invention would have no, or very few, occurrences of exchange of monomer subunits between different trimeric polypeptide complexes, and hence an implicitly improved shelf life of trimeric polypeptide complexes. Therefore, the attribute of increased thermal stability is useful, for example, in

maintaining the stability of trimeric molecules that are exposed to high temperature environments during shipping or storage.

Applicants submit that the cited prior art documents do not disclose or suggest a trimeric polypeptide complex based on a trimerising structural elements derived from tetranectin having a thermal stability on the order of that disclosed in the instant application. These unexpected properties are substantial evidence that the claimed invention was not *prima facie* obvious to one of ordinary skill in the art at the time of filing. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 19, 22-23, 68-91, 94, 98-99, 102-103, and 106-134 under 35 U.S.C. § 103(a) as allegedly unpatentable over Hoppe *et al* (WO 95/31540) in view of Thogersen *et al* (WO 94/18227), as evidenced by Kastrup *et al.* and Nielsen *et al.*

CONCLUSION


Applicants submit that claims 1, 19, 22-23, 68-91, 94, 98-99, 102-103, and 106-134 are in condition for allowance for all the reasons discussed above. Early notification of a favorable consideration and allowance of all claims are respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

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